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Survival outcomes of east Asian patients with advanced non-small cell lung cancer treated with first-line EGFR tyrosine kinase inhibitors: A network meta-analysis of real-world evidence

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Abstract

Background: The comparative efficacies of different generation tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (*EGFR*)-mutated advanced non-small cell lung cancer (NSCLC) remain largely unknown. Moreover, whether one EGFR-TKI confers superior survival remains unclear, especially in East Asians. We conducted a network meta-analysis (NMA) comparing the survival outcomes of East Asian patients with advanced NSCLC treated with first-line EGFR-TKIs.

Methods: The NMA included observational real-world evidence studies on adult patients with *EGFR*-mutated advanced NSCLC who received first (gefitinib and erlotinib), second (afatinib), or third (osimertinib) generation EGFR-TKIs as frontline therapy. Studies were identified through an online bibliographic search of Medline articles in the PubMed, SCOPUS, Web of Science, and Cochrane Library databases.

Results: For overall survival (OS), afatinib had significantly better hazard ratios (HRs) than osimertinib (HR: 0.46, 95% confidence interval [CI]: 0.23–0.91), gefitinib (HR: 0.56, 95% CI: 0.43–0.72), and erlotinib (HR: 0.71, 95% CI: 0.54–0.92). For progression-free survival (PFS), afatinib had significantly better HRs than gefitinib (HR: 0.45, 95% CI: 0.36–0.56) and erlotinib (HR: 0.63, 95% CI: 0.49–0.81). Moreover, afatinib was most likely to achieve the longest OS (81.3%), followed by erlotinib (13%), osimertinib, and gefitinib. Furthermore, afatinib was most likely to achieve the longest PFS (48.3%), followed by osimertinib (34.9%) and erlotinib.

Conclusions: This real-world evidence shows that afatinib confers better survival than other first-line EGFR-TKIs in East Asian patients with advanced NSCLC.

KEYWORDS
first-line EGFR-TKI, network meta-analysis, non-small cell lung cancer, overall survival

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide.[1] Patients with non-small cell lung cancer (NSCLC) typically present with advanced-stage disease at diagnosis and have poor prognoses. However, the introduction of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has revolutionized the management of *EGFR*-mutated advanced NSCLC, and they are currently recommended as the first-line treatment of choice in several international guidelines.[2,3] Clinical trials and real-world evidence have shown that EGFR-TKIs significantly improve progression-free (PFS)

and overall (OS) survival compared to historical standard platinum-based chemotherapy in patients with *EGFR*-mutated advanced NSCLC.[4,5] In addition, previous studies have shown that EGFR-TKIs significantly reduce the symptomatic burden and improve the quality of life of affected patients.[6]

Three generations of EGFR-TKIs are currently available. The US Food and Drug Administration approved erlotinib (a first-generation EGFR-TKI) for first-line management of *EGFR*-mutated advanced NSCLC in 2013, followed by afatinib (a second-generation EGFR-TKI) in 2013, and gefitinib (a first-generation TKI) in 2015.[7] In 2017, osimertinib (a third-generation EGFR-TKI) was approved for patients with secondary mutations making them resistant to first- and second-generation EGFR-TKIs due to its ability to irreversibly bind to primary and secondary mutations.[8] However, clinical evidence with head-to-head comparisons between first-line EGFR-TKIs remains insufficient. Most clinical trials have compared EGFR-TKIs with standard chemotherapy regimens.[9,10] Two trials compared first- and second-generation EGFR-TKIs in the first-line setting, showing more favorable outcomes with afatinib than with gefitinib[11] and erlotinib.[12]

However, real-world studies have reported conflicting results on the comparative effectiveness of first-line EGFR-TKIs in *EGFR*-mutated advanced NSCLC.[13–15] Therefore, the comparative efficacies of different EGFR-TKIs and whether one confers better clinical outcomes remain unclear, especially in East Asians. Therefore, we conducted a network meta-analysis (NMA) comparing the survival outcomes of East Asian patients with advanced NSCLC treated with first-line EGFR-TKIs. We comprehensively included all clinical data extracted and integrated from relevant databases and compared efficacy directly and indirectly through NMA.

METHODS

This study's protocol was registered with PROSPERO (ID: CRD42023388886), and this report was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement extension for NMA.[16] Since this study was based on a literature review, it did not require ethical approval or informed consent.

Eligibility criteria

This NMA included observational real-world evidence studies on adult patients with *EGFR*-mutated NSCLC who received first (gefitinib and erlotinib), second (afatinib), or third (osimertinib) generation EGFR-TKIs as frontline therapy. We restricted our inclusion criteria to articles from Taiwan, Japan, and South Korea to limit our results to East Asian populations. We only included studies reporting the survival outcomes (OS or PFS) with EGFR-TKIs published between January 2017 and December 2021. We excluded review articles, other forms of nonoriginal publications, and studies that (1) only included patients with uncommon mutations, (2) included patients with pure brain metastasis, (3) had a sample size of <100 patients, (4) had overlapping datasets, (5) had no reliable data from which to extract survival outcomes, and (6) combined interventions into groups and only reported results for aggregated groups.

Information source and search strategy

Studies were retrieved through an online bibliographic search of Medline articles in the PubMed, SCOPUS, Web of Science, and Cochrane Library databases published between January 2017 and December 2021. The bibliographic search used a combination of the following keywords: "epidermal growth factor receptor tyrosine kinase inhibitor," "EGFR TKI," "*EGFR* mutations," and "non-small cell lung cancer." This online database search was supplemented by manual searches of eligible studies' reference lists.

Study selection

The screening process had two phases: screening the titles and abstracts of unique records and screening the full text of eligible articles. Both stages were independently performed by two reviewers using predetermined criteria. Disagreements were resolved through discussion to reach a consensus. The outcome of the selection process is presented in a PRISMA flowchart (Figure 1).

Data extraction

We extracted information on the summary characteristics of the included studies and the EGFR-TKIs' baseline characteristics and survival outcomes, both in entire cohorts and in each TKI subgroup. The retrieved summary characteristics of the studies included their publication year, country of origin, design, population, sample size, and follow-up period length.

Statistical analysis

Data analyses were performed using Stata (version 16.0) and R (version 4.1.3) software. The pairwise meta-analysis used R's metan package to combine time-to-event data and the inverse variance heterogeneity (IVhet) random-effects model for dichotomous data. For articles without hazard ratios (HRs), we calculated them using Kaplan–Meier curves following Tierney et al.[17] We followed the Cochrane Handbook's guidelines for checking heterogeneity, using visual and statistical inspections such as the Chi-square and I^2 tests. Significant heterogeneity was considered a $p < 0.1$. We

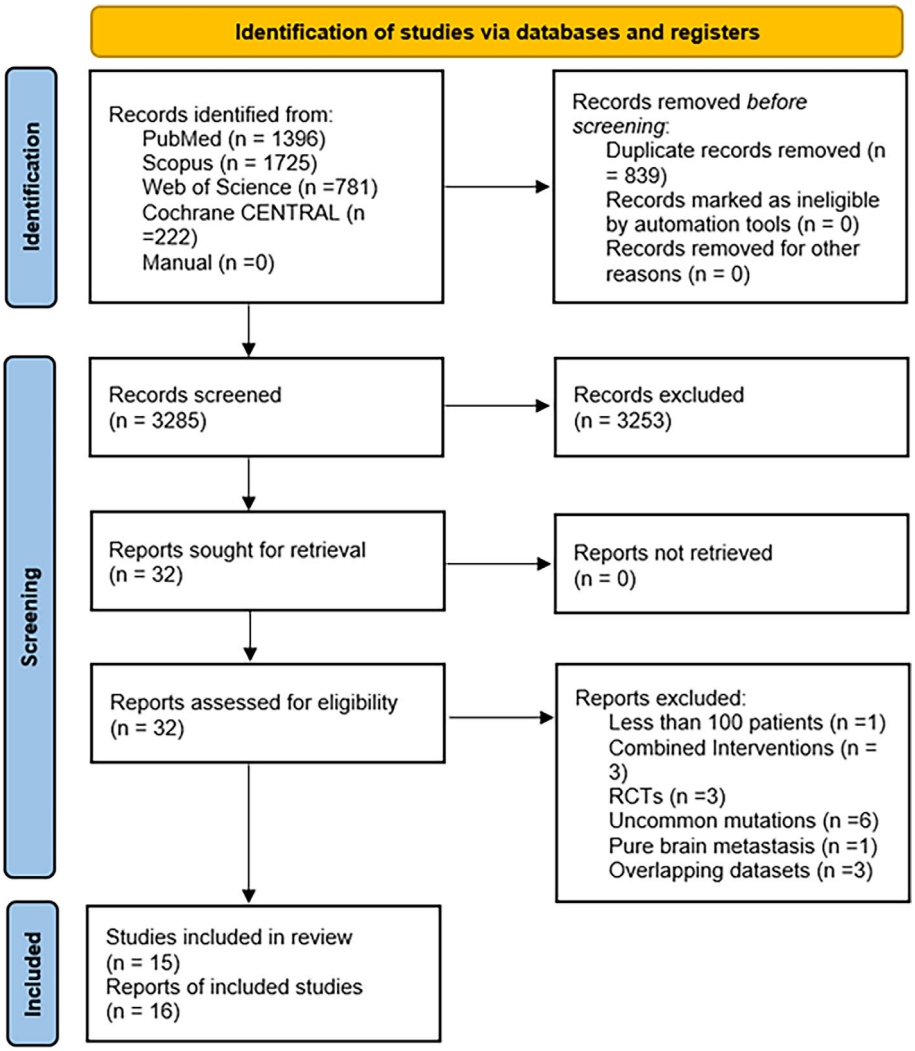

FIGURE 1 PRISMA flow chart.

performed sensitivity analyses to identify the source of heterogeneity, excluding one study at a time.

In the NMA, we used a frequentist framework and R's netmeta, mvmeta, and network_graphs packages. We used node-splitting and loop-specific approaches to identify inconsistencies in the network, where a $p < 0.05$ was considered a significant inconsistency. If no significant inconsistency was found, we used the consistency model. Then, we calculated the estimated and predictive probabilities and the relevant surface under the curve ranking area (SUCRA) to rank different interventions for each outcome. Publication bias was examined using comparison-adjusted funnel plots and Egger's regression and trim-and-fill analyses.

RESULTS

The database search strategy identified 3285 unique records, of which 3253 were excluded after title/abstract screening, leaving 32 for full-text review. Of these 32 articles, 13 were excluded because they included <100 patients ($n = 1$), combined interventions ($n = 3$), were randomized controlled trials (RCTs; $n = 3$), focused patients with uncommon mutations ($n = 6$), focused on patients with pure brain metastasis ($n = 1$), or used overlapping datasets ($n = 3$). Therefore, this NMA included 16 articles[13,14,18–31] representing 15 studies (two articles were on the same cohort[14,18]; Figure 1).

Table 1 presents the summary characteristics of the included studies. All included studies were retrospective chart reviews. Most studies were from Taiwan ($n = 10$), while three were from Japan, and two were from South Korea. The median follow-up duration of the included studies ranged from 10.3 to 23.8 months. The sample size varied substantially across the included studies, from 107 to 5940 patients. The largest two cohorts were from Taiwan ($n = 5940$) and Japan ($n = 1366$). All included studies compared afatinib with gefitinib and erlotinib.

Meta-analysis characteristics

Four interventions were analyzed (afatinib, erlotinib, gefitinib, and osimertinib), with six possible direct and indirect

TABLE 1 Summary characteristics of the included studies.

Study	Design	Study population	Follow-up (months)	Sample	Treatment arm	No.	Median OS (95% CI)	Median PFS (95% CI)
Wu et al. (2022)[19]	Retrospective cohort	Taiwan	10.5	515	Gefitinib	278	10 (8.4–11.7)	6.8 (5.6–7.9)
					Erlotinib	125	9.6 (6–13.1)	6.7 (4.6–8.7)
					Afatinib	112	16.2 (12–20.4)	11.6 (9.6–13.6)
Chang et al. (2021)[20]	Retrospective cohort	Taiwan	NR	205	Gefitinib	95	20.2 (17.6–24.9)	13.7 (11.7–15.6)
					Erlotinib	38	20 (15.9–29.4)	13.2 (9.3–18)
					Afatinib	72	29 (21.8–37.1)	21.4 (15.5–31.5)
Huang et al. (2021)[13]	Retrospective cohort	Taiwan	NR	711	Gefitinib	325	35.3 (30.4–40.2)	10.9 (9.7–12.0)
					Erlotinib	295	38.1 (31.9–44.3)	11.5 (9.9–13.1)
					Afatinib	91	40.5	16.9 (14.4–19.4)
Ito et al. (2021)[21]	Retrospective cohort	Japan	NR	550	Osimertinib	326	25.1 (NR)	NR
					Afatinib	224	36.2 (30.6–55.3)	NR
Ng et al. (2021)[22]	Retrospective cohort	Taiwan	NR	107	Gefitinib	27	19.1	13 (9.5–16.5)
					Erlotinib	33	22.9	NR
					Afatinib	47	35.6	12 (10–14)
Park et al. (2021)[23]	Retrospective cohort	Korea	NR	363	Gefitinib	122	36.8 (12.3–61.3)	10.9 (8.3–13.5)
					Erlotinib	139	23.1 (18.2–28.0)	11.2 (8.9–13.5)
					Afatinib	102	30.3 (10.0–50.6)	17.0 (11.6–22.4)
Ito et al. (2020)[24]	Retrospective cohort	Japan	18.4 18.4 18.9	1366	Gefitinib	732	32.0 (28.1–35.8)	14.4 (11.4, 17.2)
					Erlotinib	416	27.5 (23.9–31.7)	10.6 (9.3, 12.2)
					Afatinib	218	38.6 (32.2–NR)	14.4 (11.4, 17.2)
Su et al. (2020)[14]	Retrospective cohort	Taiwan	NR	853	Gefitinib	534	31.6	11.5
					Erlotinib	220	NR	11.7
					Afatinib	99	NR	16.1
Su et al. (2020)[18]	Retrospective cohort	Taiwan	NR	363	Gefitinib/ erlotinib	229	26.0 (12.9–NR)	11.2 (6.1–18.6)
					Afatinib	134	39.3 (17.2–NR)	14.1 (8.6–30.5)
Wu et al. (2020)[25]	Retrospective cohort	Taiwan	NR	125	Gefitinib	65	18.4	10.9
					Erlotinib	24	13.3	8.5
					Afatinib	36	26.4	9.6
Hsieh et al. (2019)[26]	Retrospective cohort	Taiwan	[20.3, 13.7] [18.1, 13.7] [17.3, 10.0]	5940	Gefitinib	3982	22.8 (21.9–23.5)	11.9 (11.5–12.3)
					Erlotinib	1207	23.9 (22.6–25.8)	12.7 (12.1–13.1)
					Afatinib	751	NR	15.8 (14.5–17)
Kim et al. (2019)[27]	Retrospective cohort	Korea	17.7 (95% CI, 16.5 to 18.9)	467	Gefitinib	230	NR	13.7 (12.3–15.1)
					Erlotinib	72	NR	14 (11.3–16.8)
					Afatinib	165	NR	19.1 (12.3–25.9)
Fujiwara et al. (2018)[28]	Retrospective cohort	Japan	NR	147	Gefitinib	83	27.3	9.2
					Erlotinib	36	29.3	9.8
					Afatinib	28	NR	13.1
Su et al. (2018)[29]	Retrospective cohort	Taiwan	NR	306	Gefitinib	116	22 (12.5–NR)	9.8 (5.3–16.9)
					Erlotinib	75	26.6 (15.2–45.2)	11.2 (6–19.9)
					Afatinib	115	39.1 (17.5–NR)	12.7 (8.1–28.5)
Tu et al. (2018)[30]	Retrospective cohort	Taiwan	NR	422	Gefitinib	195	NR	9.8
					Erlotinib	123	NR	11.4
					Afatinib	104	NR	12.2
Kuan et al. (2017)[31]	Retrospective cohort	Taiwan	12.1 (5.5–16.5) 11.2 (4.9–16.7) 10.3 (7.0–14.2)	448	Gefitinib	304	NR	11.4
					Erlotinib	63	NR	NR
					Afatinib	81	NR	NR

Abbreviations: CI, confidence interval; NR, not reported; OS, overall survival; PFS, progression-free survival.

comparisons. Contribution plots show the contribution matrices for the OS (Figure S1a) and PFS (Figure S1b) networks. Network maps were constructed to visualize the relative size and weight of studies involved in each direct comparison for each outcome (Figure 2). Gefitinib had the largest sample size for the NMAs of OS (largest node; Figure 2a) and PFS (Figure 2b). The direct comparison between erlotinib and gefitinib had the largest weight in the NMAs of OS and PFS.

Furthermore, we created a comparison-adjusted funnel plot for each outcome, which showed asymmetries for all interventions with a significant Egger's test indicating a

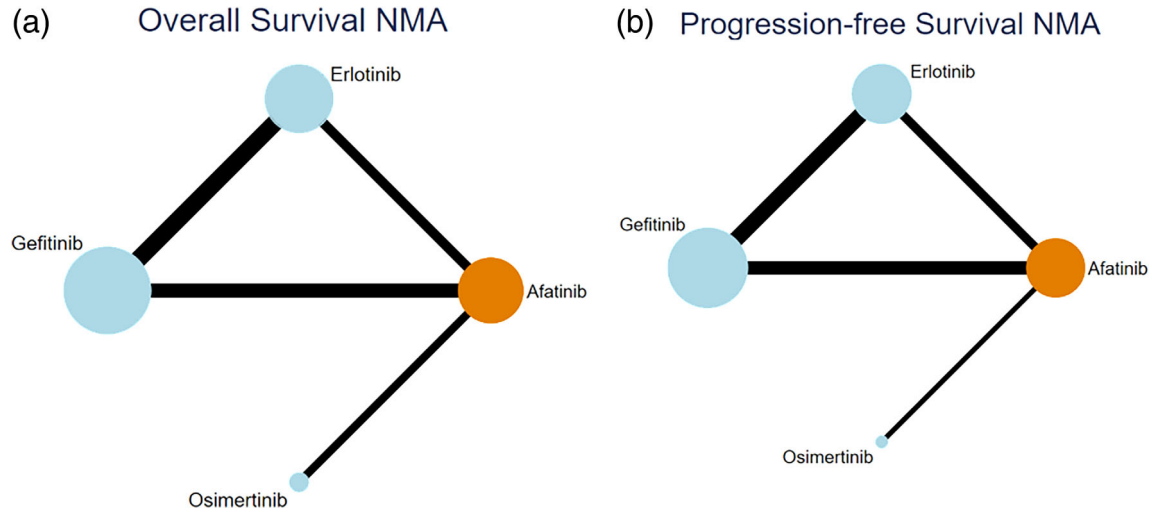

FIGURE 2 Network plots for (a) overall survival and (b) progression-free survival.

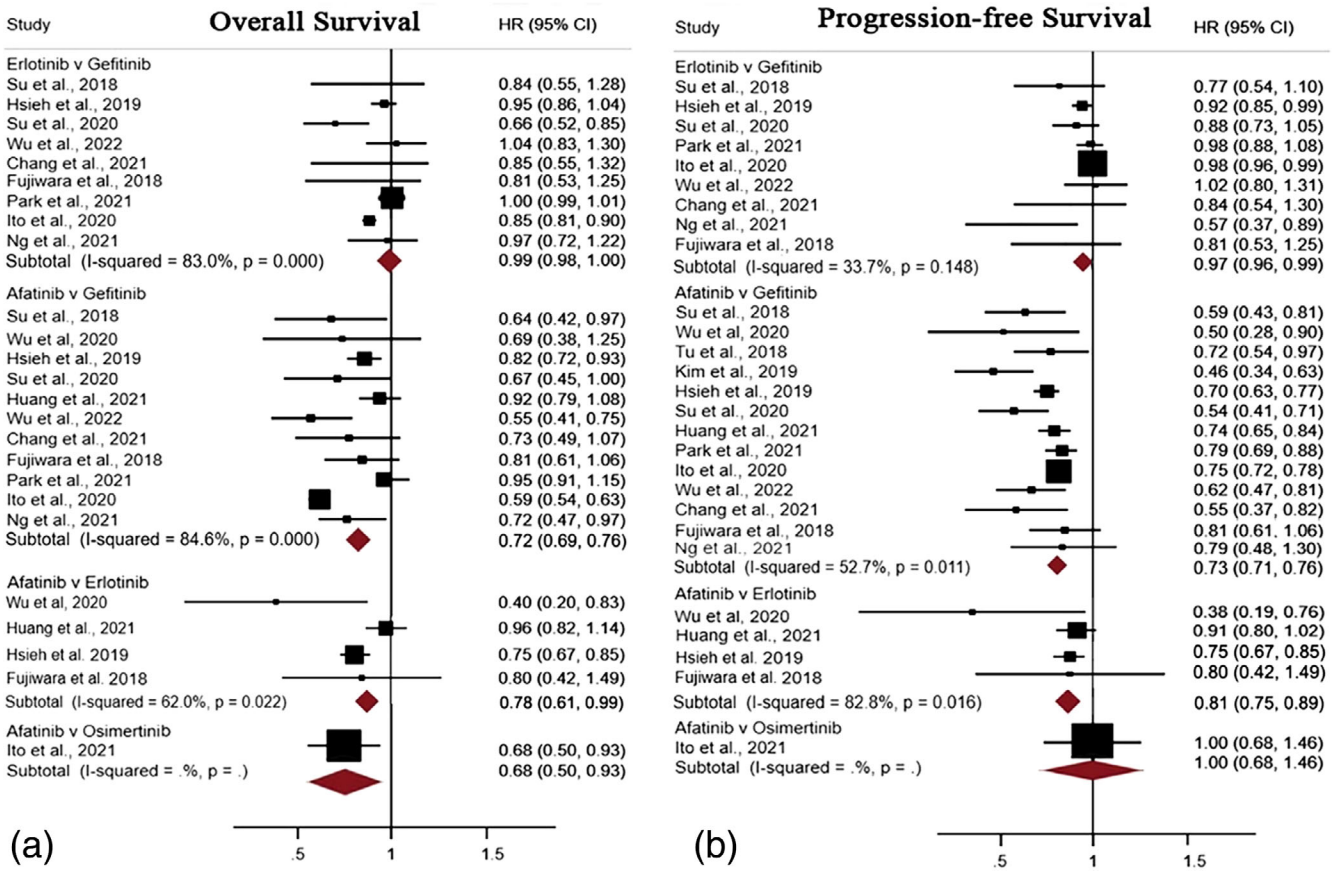

FIGURE 3 Forest plots for the pairwise comparisons of (a) overall survival and (b) progression-free survival.

small-study effect (Figure S2). The trim-and-fill analysis of publication bias imputed nine missing studies for gefitinib, eight for afatinib, and four for erlotinib.

Pairwise meta-analyses

We performed a standard pairwise IVhet meta-analysis of direct comparisons for each outcome. Since only 11 studies directly compared afatinib and erlotinib, they had pooled effect sizes. The remaining studies compared each agent with gefitinib as the reference. The results of these analyses are shown in Figure 3. Patients on afatinib had significantly better OS than those on erlotinib (HR: 0.78, 95% confidence interval [CI]: 0.61–0.99), gefitinib (HR: 0.72, 95% CI: 0.69–0.76), or osimertinib (HR: 0.68, 95% CI: 0.50–0.93). Similarly, patients on afatinib had significantly better PFS than those on gefitinib (HR: 0.73, 95% CI: 0.71–0.76) or erlotinib (HR: 0.89, 95% CI: 0.79–0.99). Moreover, patients on erlotinib had significantly better PFS than those on gefitinib (HR: 0.97, 95% CI: 0.96–0.99).

NMAs

The direct and indirect comparison results are shown as interval plots in Figure 4 and league tables with heat maps

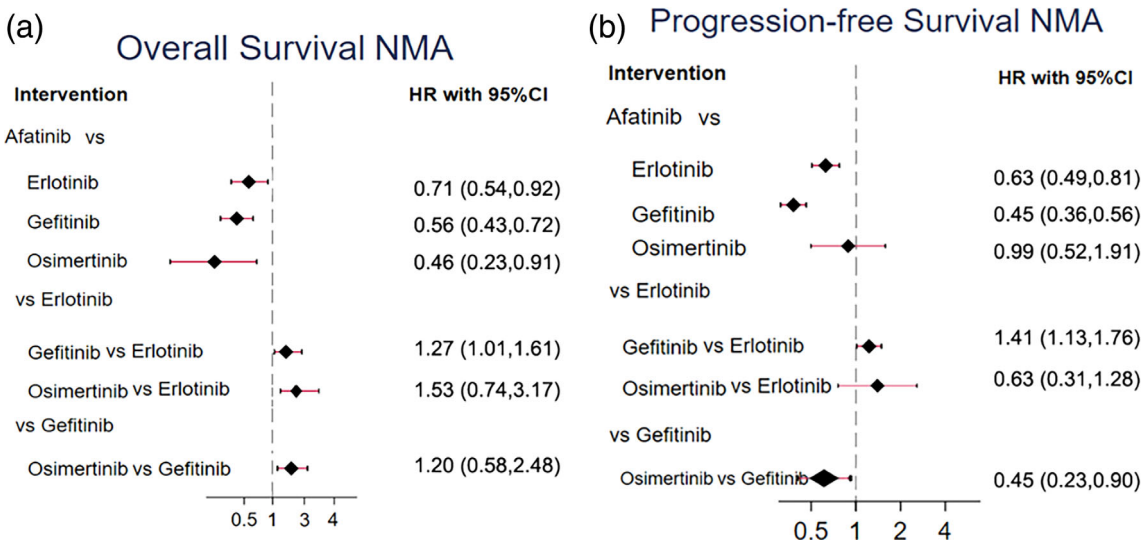

FIGURE 4 Interval plots for (a) overall survival and (b) progression-free survival.

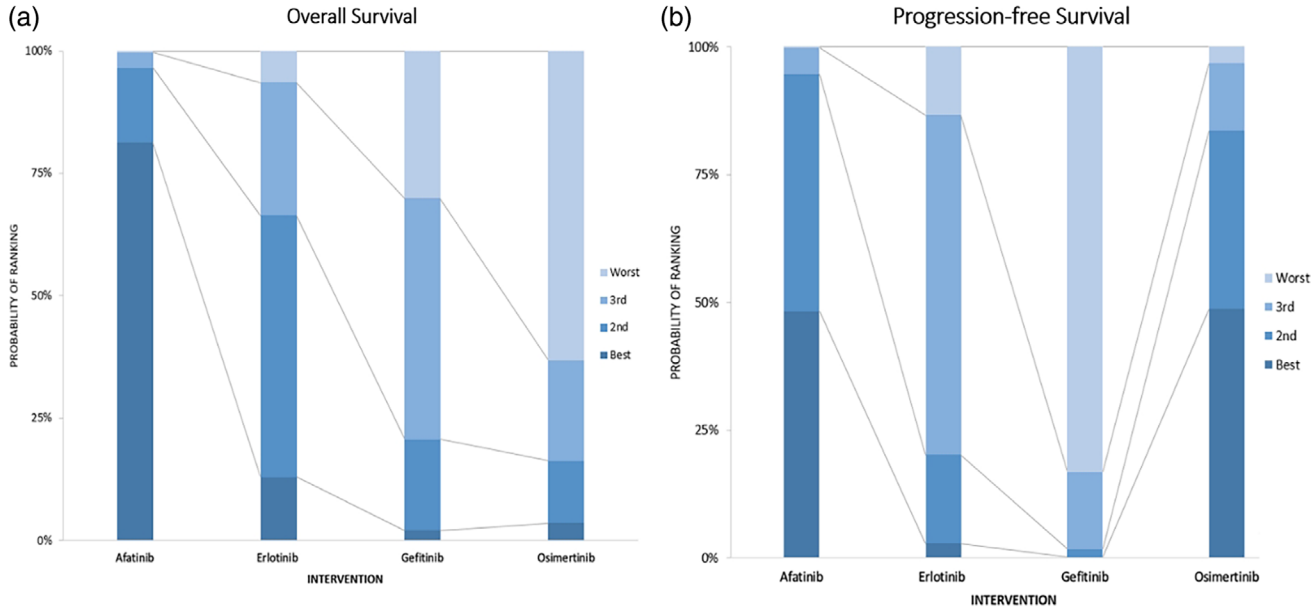

FIGURE 5 Probability rankings for (a) overall survival and (b) progression-free survival. The interventions were ranked according to their likelihood of achieving the longest survival; the "best" legend denotes that the intervention ranked the most effective in prolonging survival, and the "worst" legend denotes that the intervention ranked the least effective in prolonging survival.

in Figure S3. For OS, afatinib had significantly better HRs than osimertinib (HR: 0.46, 95% CI: 0.23–0.91), gefitinib (HR: 0.56, 95% CI: 0.43–0.72), and erlotinib (HR: 0.71, 95% CI: 0.54–0.92). For PFS, afatinib also had significantly better HRs than gefitinib (HR: 0.45, 95% CI: 0.36–0.56) and erlotinib (HR: 0.63, 95% CI: 0.49–0.81).

The ranking probabilities of each outcome's efficacy for each intervention are shown in Figure 5. Afatinib was most likely to achieve the longest OS (81.3%), followed by erlotinib (13%), osimertinib, and gefitinib. Afatinib was also the most likely to achieve the longest PFS (48.3%), followed by osimertinib (34.9%) and erlotinib. Based on the two-dimensional cluster ranking of average SUCRA values, which combine the probabilities of achieving the best OS and PFS (Figure S4), afatinib was most likely to be ranked as the most effective intervention, followed by erlotinib, gefitinib, and osimertinib.

DISCUSSION

This systematic review and NMA showed that among the East Asian NSCLC patients, the second-generation EGFR-TKI (afatinib) group had significantly longer median OS and PFS than the first (gefitinib and erlotinib) and third (osimertinib) generation EGFR-TKI groups. Moreover, the first-generation EGFR-TKI erlotinib was associated with a longer OS than gefitinib and osimertinib. However, PFS did not differ significantly between erlotinib and osimertinib. The agreement between the pairwise and network analyses highlights the consistency of these findings among the individual and pooled studies. These findings indicate that using the second-generation EGFR-TKI afatinib as the first-line treatment in East Asian patients with NSCLC could improve their survival outcomes compared to other generations.

The various selection criteria and analytical methods used in previous systematic reviews and meta-analyses on NSCLC make it challenging to compare them directly with our study.[32,35] While the three globally sanctioned EGFR-TKIs (afatinib, erlotinib, and gefitinib) have generally not shown any significant differences in OS, afatinib was slightly more favorable in a few studies.[32,35] Holleman et al. showed that osimertinib conferred better OS than afatinib, erlotinib, and gefitinib, while dacomitinib had a slight tendency towards improvement.[32] Both osimertinib and dacomitinib conferred better PFS than other EGFR-TKIs.[32–35] Lin et al. did not find significant differences in dacomitinib and osimertinib efficacy between general and Asian populations.[33]

Yang et al. conducted a meta-analysis comparing afatinib, gefitinib, and erlotinib in patients with NSCLC.[36] Their findings showed that gefitinib and erlotinib conferred similar overall response rates, OS, PFS, and disease control. These effects did not differ significantly among patients with different treatment lines, ethnicity, or *EGFR* mutations. They showed that afatinib was comparable to gefitinib and erlotinib in the first-line setting for *EGFR*-mutated NSCLC. Nevertheless, afatinib was more effective than erlotinib as a second-line treatment in patients with advanced NSCLC. They explained the similar efficacies for erlotinib and gefitinib through the higher bioavailability of erlotinib (150 mg/day) than gefitinib (250 mg/day, one-third of the maximum tolerated dose). However, despite its greater bioavailability, erlotinib did not show superior anticancer efficacy to gefitinib. This finding may be attributable to gefitinib's significant accumulation in tumor tissue compared to plasma, differing from erlotinib's clinical pharmacokinetics. Therefore, gefitinib may show greater tumor tissue penetration and accumulation, leading to comparable efficacy despite its lower bioavailability.[37–40]

Our findings differ from Yang et al., potentially reflecting differences in inclusion criteria. While Yang et al. included RCTs and observational studies without ethnicity restrictions, our study only included real-world evidence in East Asian patients with advanced NSCLC. In our analysis, the superiority of afatinib over gefitinib and erlotinib might reflect it being a pan-human EGFR (HER) inhibitor, targeting EGFR and other HER family members, such as HER2 and HER4. This broader inhibition profile may lead to better tumor growth control and more durable responses than EGFR-specific inhibitors such as gefitinib and erlotinib. Moreover, afatinib has also been shown to be effective in patients with acquired resistance to first-generation EGFR-TKIs.[41,42]

Osimertinib is a newly approved EGFR-TKI for treating advanced EGFR-positive NSCLC. RCTs and NMAs have confirmed osimertinib's efficacy.[32,33,43] The introduction of osimertinib and comparative trials have prompted significant studies on the most effective use of EGFR-TKIs in clinical practice. The NMA of 49 articles by Franek et al. comprising 15 RCTs and 34 comparative studies, indicated that osimertinib conferred significantly improved PFS than afatinib, erlotinib, and gefitinib and showed a favorable PFS trend compared to dacomitinib.[44] These findings contradict our study which showed that osimertinib was associated with the lowest OS and PFS.

This study's results have important clinical implications. While there is currently no strong evidence showing significant differences in efficacy between gefitinib, erlotinib, and afatinib, gefitinib appears to be the preferred first-line treatment option for patients with *EGFR*-mutated NSCLC due to its favorable safety profile. However, it should be noted that these agents may not always be optimal for their respective settings. Clinical decision-making should consider factors such as the patient's physical status, available resources, and personal values, which can complicate treatment choices. Different agent costs and reimbursement or discounting schemes may also vary within health systems. Therefore, treatment selection should be carefully considered on a case-by-case basis, considering each patient's unique circumstances and needs.

While our study provides valuable insights into the optimal first-line treatment for patients with *EGFR*-mutated advanced NSCLC, we acknowledge some limitations. First,

the lack of RCTs in our analysis may have limited the quality of evidence generated. Second, the number and quality of the included studies were relatively low, which could have also impacted the strength of the evidence. Third, we did not perform a subgroup analysis to examine the impact of disease status, age, mutation type, and patient residency on treatment outcomes. This information could have provided further insights into factors influencing treatment efficacy and improved the generalizability of our findings. Future studies addressing these limitations will help validate our results and improve the clinical management of patients with *EGFR*-mutated NSCLC.

In conclusion, this NMA provides evidence to aid clinicians in selecting a different generation of EGFR-TKIs as the optimal first-line treatment regimen for patients with *EGFR*-mutated advanced NSCLC, particularly those with East Asian ancestry. Real-world evidence shows that afatinib confers the best survival outcomes compared to other first-line EGFR-TKIs in East Asian patients with NSCLC. Based on pairwise comparisons from several studies, afatinib ranked highest for PFS and OS among first-line EGFR-TKIs. It is crucial to interpret our study's results in light of its limitations and the evolving treatment landscape. Future studies, including RCTs and prospective observational studies, should continue investigating the efficacy and comparative effectiveness of different EGFR-TKIs, including osimertinib, in various *EGFR*-mutated NSCLC patient populations.

AUTHOR CONTRIBUTIONS

Huang-Chih Chang: conception/design; collection and/or assembly of data; manuscript writing. Kuo-Tung Huang: collection and/or assembly of data. Chia-Cheng Tseng and Yu-Mu Chen: data analysis and interpretation. Chien-Hao Lai, Yu-Ping Chang, and Yung-Che Chen: provision of study material. Hung-Yi Chuang and Chin-Chou Wang: data analysis and interpretation; final approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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